Patent
Attorney's Docket No. 012712-014

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	
	)	
Darrell R. ANDERSON et al	)	Group Art Unit: 1816
	)	
Application No.: 08/149,099	)	Examiner: R. Schwadron
	)	
Filed: November 3, 1993	)	
	)	
For: THERAPEUTIC APPLICATION OF CHIMERIC AND RADIO-LABELED ANTIBODIES TO HUMAN B...	)	

SECOND DECLARATION UNDER 37 C.F.R. § 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Darrell R. Anderson, declare and state as follows:

THAT, I have a Doctorate of Biochemistry from Oklahoma State University;

THAT, a copy of my Curriculum Vitae is attached hereto;

THAT, I am the inventor of the subject matter disclosed and claimed in the above-referenced application and I have reviewed and am familiar with the contents of U.S. Patent Application Serial No. 08/149,099;

THAT, I have reviewed and am familiar with the Examiner's rejection of the claims alleging that the disclosure is purportedly unpatentable over each of Robinson et al. (U.S. Patent Serial No. 5,500,362) and Robinson et al. (WO 88/04936). More specifically, that I understand that the Examiner has concluded that the anti-CD20

chimeric antibody which is the subject of this application would appear to be functionally equivalent to that disclosed in the above-identified Robinson patent. However, based on the following, I am of the opinion that the Examiner's conclusion is unsustainable as the chimeric anti-CD20 antibody which is the subject of the present invention exhibits properties which were totally unexpected and which moreover render it uniquely suited for use as a therapeutic, in particular for treatment of B cell lymphoma.

THAT, based on the following, I do not agree with the Examiner's conclusion.

THAT, a chimeric anti-CD20 antibody (IDEC-C2B8), consisting of human IgG1-K constant regions was developed by IDEC pharmaceuticals for the treatment of non Hodgkins B cell lymphoma.

THAT, the IDEC-C2B8 antibody lyses CD20+ cells *in vitro* via complement and antibody-dependent cell-mediated lysis.

THAT, preclinical studies have shown that the antibody selectively depletes B cells in blood, lymph nodes and bone marrow in macaque monkeys. Furthermore, the antibody has been shown to be highly effective in treating patients with relapsed low grade lymphoma, producing marked response rates in very sick patients. In my opinion, these clinical results were unexpected and could not have been reasonably predicted based on *in vitro* properties.

THAT, while many of the *in vitro* properties of IDEC-C2B8 are shared with other anti-CD20 antibodies, a remarkable and apparently unique property of IDEC-C2B8 is the ability to deplete CD20 positive cells *in vivo* with such low doses. As low as 0.4 mg/kg was effective in depleting better than 95 percent of B cells in the peripheral blood of

monkeys. This was a surprising result which supports the claims that C2B8 has unique properties beyond what is shared by other anti-CD20 antibodies. While it is difficult to compare directly other chimeric anti-CD20 antibodies because none have been tested *in vivo* as extensively as C2B8, the available evidence would suggest that C2B8 has a much stronger effector depleting property than other chimeric antibodies which is apparently attributable to exceptionally strong Fc receptor binding.

THAT, the following description of an antibody FcRII binding assay conducted under my supervision demonstrates that this enhanced Fc receptor binding is apparently the result of the combining of a unique mouse variable region sequence having a unique amino acid sequence with the human IgG1 constant region:

Binding of IDEC-C2B8 to Human FcγRII Transfected Cells

FcγRII transfected CDW32 cells were attached to a 96 well plate pre-coated with Poly-L-Lysine. Due to the lack of soluble antigen, IDEC-C2B8 and the control antibodies were evaluated in the absence of CD20 by serial dilutions at concentrations ranging from 2 to 0.025 μg/mL in wells of the cell coated plate. The amount of antibody bound to the FcγRII receptors was detected by incubation with Goat Anti-Human IgG-HRP (1:2000) reagent. Peroxidase substrate reagent (TMB) was added and absorbance derived from the color forming reaction was measured at 450 nm with an ELISA plate reader. The results in Figure 1 show that IDEC-C2B8 has exceptionally strong binding to low affinity FcγRII receptors, in contrast to the positive control human IgG1 isotype and the negative control human IgG4 isotype.

Conclusion

In my expert opinion, these results are unexpected, in view of the fact that low affinity receptor binding by antibodies is usually reduced in the absence of antigen binding. By contrast, these results indicate that IDEC-C2B8 has an unusually strong affinity for this type of receptor which may be even further enhanced *in vivo* on binding of antigen. The results are highly supportive of the claim that IDEC-C2B8 can mediate effector cell functions *in vivo* with effector cells expressing FcγRII receptors in a manner unequaled by other CD20 antibodies. Moreover, these results suggest that this antibody does not function equivalently to other chimeric anti-CD20 antibodies.

In my opinion, it would be highly unreasonable to expect that other anti-CD20 antibodies including the chimeric antibodies of the Robinson et al., if compared in this assay, would show equivalent behavior especially because comparison to totally human antibodies of the same isotype as seen in the controls, are not equivalent. In fact, the murine antibody from which the variable region was derived shows no more binding in this assay than the negative control above. Therefore, the subject chimeric antibody shows behavior uncommon to any other antibody tested including other chimeric engineered constructs which differ from C2B8 only in the variable region which is contained therein. This property, therefore, appears to be attributable to the particular variable region contained in the C2B8 antibody. However, it is noted that the assay shown above does not measure or in any way relate to antigen specificity, only the ability to bind to human FcRII receptors. In my opinion, it is this property that is the most unique of the C2B8 effector properties, and may explain the unparalleled ability of the

subject antibody to mediate such extensive depleting behavior, *in vivo*. As a expert in the art, I can well attest to the fact that type II receptor binding mediated through macrophages and monocytes following specific antibody binding to target cells, is well regarded by many skilled in the art to be the most potent of all possible *in vivo* depleting mechanisms.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 11/27/96 By: Darrell R. Anderson
Darrell R. Anderson

Figure 1

Binding of IDEC-C2B8 to CDW32 Mouse Fibroblast Cells Transfected with Human Low Affinity FcγRII Membrane Receptors

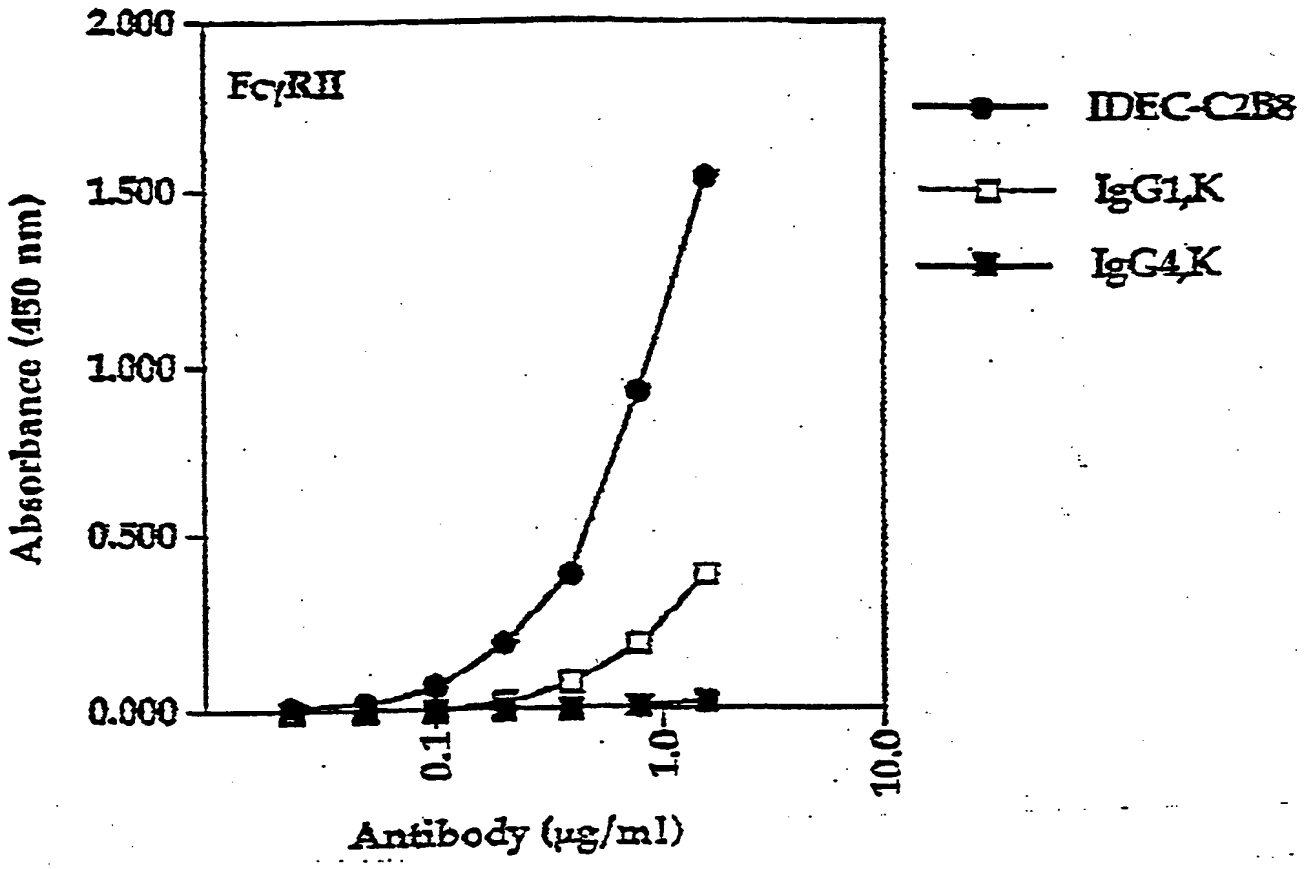

Figure 1. IDEC-C2B8 antibody was serially diluted in the absence of CD20, along with positive and negative isotype control human IgG1 and IgG4 antibodies. Aliquots were added in triplicate to sets of wells each containing FcγRII (human type II Fc receptor) transfected CDW32 mouse L cells. Binding of antibodies to Fc receptors was determined by ELISA. These results indicate that IDEC-C2B8 binds much more strongly to the low affinity human FcγRII receptor than typical human IgG1 antibodies with similar receptor binding sites.

CURRICULUM VITAE

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Summary of Professional Experience:

Management

1993 - Present	Director, Antibody Discovery, IDEC Pharmaceuticals Corporation, San Diego, CA 92121
1988 - 1993	Senior Scientist, Department of Cellular Immunology, IDEC Pharmaceuticals Corporation, La Jolla, CA 92037
1986 - 1988	Project Scientist, Department of Immunochemistry, Synbiotics Corporation, San Diego, CA 92127
1971 - 1972	Decommissioning Supervisor and Troubleshooter, U.S. Naval Shipyard, Long Beach, CA
1970 - 1971	Executive Officer/Navigator, U.S. Navy, USS Advance (MSO 510), Long Beach, CA
1967 - 1969	Chief Engineer, U.S. Navy, USS Advance (MSO 510), Long Beach, CA

Research

1988 - 1993	Senior Scientist, Cellular Immunology, IDEC Pharmaceuticals Corporation, La Jolla, CA 92037
1986 - 1988	Project Scientist, Veterinary Vaccines, Department of Immunochemistry, Synbiotics Corporation, San Diego, CA, 92127
1982 - 1986	Research Assistant Professor, Department of Biochemistry, University of Arizona, Tucson, AZ 85724
1977 - 1981	Fellow, National Cancer Institute, Dept. of Biochemistry, University of Arizona, Tucson, AZ 85724
1972 - 1976	Graduate Research Assistant, Department of Biochemistry, Oklahoma State University, Stillwater, OK 74074

Education:

B.S., Oklahoma State University, Major in Biochemistry, July, 1972

Ph.D. in Biochemistry, Oklahoma State University, Stillwater Oklahoma, December, 1976

Honors:

Sigma Xi Graduate Student Research Award for Outstanding Research in the Division of Physical and Biological Sciences. Oklahoma State University, 1976.

NIH Postdoctoral Fellowship 1977-1981.

Publications:

1. **Anderson, D.A.,** Grillo-López, A., Varns, C., Chambers, K. and Hanna, N. 1996. Targeted Anti-Cancer Therapy Using Rituximab Chimeric Anti-CD20 Antibody (IDEC-C2B8) in the Treatment of Non-Hodgkin's B Cell Lymphoma. *Trans. Biochem. Society (in press).*

2. Reff, M.E., K. Carner, K.S. Chambers, P.C. Chinn, J.E. Leonard, R. Raab, R.A. Newman, N. Hanna, and **D.R. Anderson.** 1994. Depletion of B Cells *In Vivo* by a Chimeric Mouse Human Monoclonal Antibody to CD20. *Blood. 83:435-445.*

3. Newman, R.A., J. Alberts, **D.R. Anderson,** F. Norton, R. Raab, M. Reff, and N. Hanna. 1992. Idiotype Network Responses to Murine IgG3 Anti-Carbohydrate Antibodies. *J. Immunotherapy. 11:267-273.*

4. **Anderson, D.R.** and R.E. McCoobery. 1992. Idiotype Network Responses to Murine Immunoglobulin G3 Anti-Carbohydrate Antibodies. *Journal of Immunotherapy. 11:267-273.*

5. Osir, E.O., **D.R. Anderson,** W.J. Grimes, and J.H. Law. 1986. Studies on the Carbohydrate Moiety of Vitellogenin From the Tobacco Hornworm, *Manduca Sexta. Insect Biohem. 16:471-478.*

6. Ryan, R.O., **D.R. Anderson,** W.J. Grimes, and J.H. Law. 1985. Arylphorin From *Manduca Sexta:* Carbohydrate Structure and Immunological Studies. *Arch. Biochem. Biophys. 243:115-124.*

7. **Anderson, D.R.,** P.H. Atkinson, and W.J. Grimes. 1985. Major Carbohydrate Structures at Five Glycosylation Sites on Murine IgM Determined by High Resolution H-NMR Spectroscopy. *Arch. Biochem. Biophys. 243:605-618.*

8. **Anderson, D.R.**, P. Samaraweera, and W.J. Grimes. 1983. Incomplete Glycosylation of ASN 563 in Mouse Immunoglobulin M. *Biochem. and Biophys. Res. Comm. 116:771-776.*

9. **Anderson, D.R.**, and W.J. Grimes. 1982. Heterogeneity of Asparagine-linked Oligosaccharides of Five Glycosylation Sites on Immunoglobulin M Heavy Chain from Mineral Oil Plasmacytoma 104E. *The Journal of Biological Chemistry. 257:14858-14864.*

Patents:

(1993) "Therapeutic Application of Y^{90} Labeled Pan B Antibodies to Human B Lymphocte Restricted Differentiation Antigen for Treatment of B Cell Lymphoma," P. Chinn, **D. R. Anderson,** J. Leonard, and N. Hanna.

(1991) "Therapeutic Application of Chimeric Antibody to Human B Lymphocyte Restricted Differentiation Antigen for Treatment of B Cell Lymphoma," **D. R. Anderson,** R. Newman, J. Leonard, N. Hanna, and M. Reff.

(1987) "Method for Early Selection of Internal Image Anti-Idiotype Antibodies," **D.R. Anderson,** M. Vodian, and E. Maggio.

Book Chapters:

1. Grimes, W.J. and **D.R. Anderson.** Nutritional Requirements of Animal Cells in Culture. 1981. *R. Ham, Ed., Cambridge University Press, pp. 388-400.*

2. Muller, S. , H. Kohler, and **D.R. Anderson.** Rationale for the Design of Anti-idiotypic Antibody Vaccines in Recombinant DNA Vaccines. 1992. *R.E. Isaacson, Ed., Marcel Dekker, Inc., New York, pp. 335-367.*

3. **Anderson, D.R.,** H. Köhler, and S. Muller. 1992. Biomodulation with Network Epitopes. In *The Biomodulation of Cancer, M. Mitchell, Ed., Pergamon Press, Inc. Elmsford, NY, pp. 155-171.*

Recent Abstracts and Presentations:

Primatized Antibodies for Repeat Dose Immunotherapy. *Second International Conference on Commercializing Human Monoclonal Antibodies,* (1994), D.R. Anderson, IDEC Pharmaceuticals Corporation.

Monoclonal Anti-CD20 Antibody (IDEC-C2B8) Therapy of B-Cell Non Hodgkin's Lymphoma--Pre-Clinical Development and Early Clinical Results. *NCI-EORTC Meeting (1994),The Netherlands,* A.J. Grillo-Lopez, V. Carrali, J.E. Leonard, B.K. Dallaire, D.R. Anderson, and M.E. Reff.

IDEC-C2B8: A Promising New Monoclonal Anti-CD20 Antibody for the Treatment of B-Cell Non-Hodgkin's Lymphoma. A.J. Grillo-Lopez, J.E. Leonard, V. Carrali, B.K. Dallaire, D.R. Anderson, and M.E. Reff.

Preclinical and Early Clinical Development of the Anti-CD20 Monoclonal Antibody IDEC-C2B8. *Ninth International Conference on Monoclonal Antibody Imunoconjugates for Cancer, San Diego, CA, March 3-5, 1994,* A.J. Grillo-Lopez, J.E. Leonard, V. Carrali, B.K. Dallaire, D.R. Anderson, and M.E. Reff.

Regulation of Lymphocyte Activation with PRIMATIZED® Antibodies: Therapeutic Applications in Chronic Autoimmune Diseases. *IBC's Second Annual Industry Conference; Psoriasis; Latest Advances in Understanding and Therapeutic Development. November 12-13, 1996, Washington, D.C.* D.R. Anderson.

Patent
Attorney's Docket No. 012712-014

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of)
)
Darrell R. ANDERSON et al) Group Art Unit: 1816
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Application No.: 08/149,099) Examiner: R. Schwadron
)
Filed: November 3, 1993)
)
For: THERAPEUTIC APPLICATION OF)
CHIMERIC AND RADIOLABELED)
ANTIBODIES TO HUMAN B)
LYMPHOCYTE RESTRICTED)
DIFFERENTIATION ANTIGEN FOR)
TREATMENT OF B CELL LYMPHOMA)

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Darrell R. Anderson, declare and state as follows:

(1) That I am the same Darrell R. Anderson named as an inventor of the above-identified application.

(2) That I am aware of the facts that led up to the subject invention.

(3) That I am further familiar with the claims being considered by the Examiner in the above-identified application.

(4) That based on such review, and my personal knowledge, I can attest to the fact that William E. Rastetter made an inventive contribution to the subject application. Specifically, William E. Rastetter, Ph.D. was involved in the initial conception relating to the usage of the subject chimeric anti-CD20 antibody as a pharmaceutical for the treatment of B cell lymphoma. Also, Dr. Rastetter was involved in the initial

conception relating to the usage of this antibody in combination with a radiolabeled non-chimeric anti-CD20 antibody. Further, I can attest to the fact that the contribution of John E. Leonard solely relates to the combined usage of the subject chimeric anti-CD20 antibody with a radiolabeled non-chimeric (murine) antibody (from which the subject chimeric antibody was derived) as a therapeutic for treatment of B cell lymphoma.

(5) I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

5/15/97
Date

Darrell R. Anderson
DARRELL R. ANDERSON

Patent
Attorney's Docket No. 012712-105

IN THE EUROPEAN PATENT OFFICE

In re Patent Application of)
IDEC Pharmaceuticals Corp.)
Application No.: 94901444.3)
Filed: June 9, 1995)
For: THERAPEUTIC APPLICATION OF CHIMERIC AND RADIOLABELED ANTIBODIES TO HUMAN B LYMPHOCYTE RESTRICTED DIFFERENTIATION ANTIGEN FOR TREATMENT...))

DECLARATION OF DARRELL R. ANDERSON

The European Patent Office
P B 5818 Patentlaan 2
2280 HV Rijswijk (ZH)
Netherlands

Sir:

I, Darrell R. Anderson, declare and state as follows:

(1) I reside at 1851 Navajo Place, Escondido, California 92029.

(2) I am the same Darrell R. Anderson who is an inventor on the above-identified application. I am also the same Darrell R. Anderson who is an author on "Immunoreactivity and Effector Function Associated with a Chimeric Anti-CD20 Antibody," Anderson et al, *The 2nd Annual IBC International Conference on Antibody Engineering* (December 16-18, 1991 (hereinafter "the Anderson abstract" or "the Anderson reference").

(3) The Anderson reference is an abstract which was presented at the IBC International Conference. This abstract generally relates to the C2B8 and the 2B8 antibodies. More particularly, and as reflected by the title of the abstract, the Anderson reference

relates to the immunoreactivity and effector functions associated with the C2B8 antibody. The abstract further describes that the C2B8 antibody is a chimeric antibody containing human constant regions and murine variable regions which binds to the human CD20 antigen. The abstract further discloses that the 2B8 antibody is the murine anti-CD20 antibody from which the variable regions contained in the C2B8 antibody were derived. Also, the Anderson abstract contains information relating to the potential usage of the C2B8 antibody for the treatment for B cell lymphoma.

(4) However, as discussed in the letter submitted to the European Patent Office on September 5, 1995, the Anderson abstract does not contain sufficient information to enable one skilled in the art to synthesize or otherwise obtain the C2B8 or the 2B8 antibodies. For example, this abstract does not contain any amino acid or DNA sequence information relating to the C2B8 or the 2B8 antibody. Moreover, no amino acid or DNA sequence information relating to either the C2B8 or the 2B8 antibody was reported in the literature or otherwise publicly disseminated prior to the November 13, 1992 priority date of this application. Furthermore, neither the C2B8 antibody or the 2B8 antibody, or cell lines which produce either of these antibodies were made publicly available prior to the November 13, 1992 priority date of this application.

The undersigned inventor declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false

Application No. 94901444.3

statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statement may jeopardize the validity of the application or any patent issuing thereon.

Date: 2/1/96

Darrell R. Anderson

Darrell R. Anderson, PhD.

Patent
Attorney's Docket No. 012712-014

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	
Darrell R. ANDERSON et al	Group Art Unit: 1816
Application No.: 08/149,099	Examiner: R. Schwadron
Filed: November 3, 1993	
For: THERAPEUTIC APPLICATION OF CHIMERIC AND RADIO-LABELED ANTIBODIES TO HUMAN B...	

FIRST DECLARATION UNDER 37 C.F.R. § 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Darrell R. Anderson, do hereby declare:

THAT, an abstract entitled "Immunoreactivity and Effector Function Associated with a Chimeric Anti-CD20 Antibody" was published in The Second Annual IBC International Conference on Antibody Engineering, held December 16-18, 1991 in San Diego, CA and coauthored by Darrell R. Anderson, Robert E. McCoobery, Mitchell Reff, Roland Newman, Syamal Raychaudhuri and Nabil Hanna;

THAT, I am familiar with the claims being considered by the Examiner in the above-identified application;

Application Serial No. 08/149,099
Attorney's Docket No. 012712-014

THAT, to the extent that the abstract cited above describes the invention claimed in the above-referenced patent application, this article describes my own work and that of co-inventors Mitchell Reff, Roland Newman and Nabil Hanna;

THAT, abstract co-authors Robert E. McCoobery and Syamal Raychaudhuri merely acted under my direction and did not contribute to the conception of the invention disclosed and claimed in the above-referenced patent application;

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 11/26/96

By: _____
Darrell R. Anderson